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Comparison of Outcomes of Allogeneic Transplantation for Chronic Myeloid Leukemia with Cyclophosphamide in Combination with Intravenous Busulfan, Oral Busulfan, or Total Body Irradiation

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Cyclophosphamide (Cy) in combination with busulfan (Bu) or total body irradiation (TBI) is the most commonly used myeloablative conditioning regimen in patients with chronic myeloid leukemia (CML). We used data from the Center for International Bone Marrow Transplantation Research to compare outcomes in adults who underwent hematopoietic cell transplantation for CML in first chronic phase after myeloablative

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Busulfan
Total body irradiation

conditioning with Cy in combination with TBI, oral Bu, or intravenous (i.v.) Bu. Four hundred thirty-eight adults received human leukocyte antigen (HLA)-matched sibling grafts and 235 received well-matched grafts from unrelated donors (URD) from 2000 through 2006. Important differences existed between the groups in distribution of donor relation, exposure to tyrosine kinase inhibitors, and year of transplantation. In multivariate analysis, relapse occurred less frequently among patients receiving i.v. Bu compared with TBI (relative risk [RR], .36; $P = .022$) or oral Bu (RR, .39; $P = .028$), but nonrelapse mortality and survival were similar. A significant interaction was detected between donor relation and the main effect in leukemia-free survival (LFS). Among recipients of HLA-identical sibling grafts, but not URD grafts, LFS was better in patients receiving i.v. Bu (RR, .53; $P = .025$) or oral Bu (RR, .64; $P = .017$) compared with TBI. In CML in first chronic phase, Cy in combination with i.v. Bu was associated with less relapse than TBI or oral Bu. LFS was better after i.v. or oral Bu compared with TBI.

INTRODUCTION

Tyrosine kinase inhibitors (TKIs) have replaced allogeneic hematopoietic cell transplantation (HCT) as initial therapy of patients with chronic myeloid leukemia (CML). Nevertheless, many patients with CML eventually receive an allotransplant. Determining the best pretransplantation conditioning regimen is important.

Cyclophosphamide (Cy) combined with total body irradiation (TBI) has historically been the standard pretransplantation conditioning regimen [1-4]. The combination of Cy with a fixed dose of oral busulfan (BuCy) has also proven effective in CML [5]. A randomized comparison of Cy/TBI to BuCy in patients with CML undergoing human leukocyte antigen (HLA)-identical sibling transplantation reported comparable relapse, leukemia-free survival (LFS), and overall survival (OS). BuCy was better tolerated, however, with shorter hospitalization and less acute graft-versus-host disease (GVHD) [6]. A second randomized study reported similar outcomes but with fewer relapses in the BuCy cohort [7].

The development of an assay for plasma Bu was initially reported in 1983 [8], but an assay was not commercially available until 1996 [9]. Studies of Bu kinetics revealed that oral Bu is erratically absorbed and that oral administration of a fixed dose results in wide variations in plasma Bu levels [10-13]. Low plasma levels are associated with increased risks of graft failure and relapse, and high levels are associated with increased toxicity [10-12]. Dose adjustment of oral Bu, based on plasma levels after the initial dose, decreases the variability and may improve outcomes [14]. An intravenous (i.v.) formulation of Bu was developed and its use in patients was first reported in 2002 [15,16]. It provides complete bioavailability, much more consistent plasma levels, less acute toxicity, and lower 100-day mortality than an oral fixed dose [15,16]. Although a retrospective study in acute myeloid leukemia (AML) from the European Group for Blood and Marrow Transplantation failed to show significant differences in outcome [17], a recent large retrospective study in patients with AML in first remission from the Center for International Bone Marrow Transplant Research (CIBMTR) reported significantly less nonrelapse mortality (NRM) and late relapse, and better LFS and OS with Cy in combination with i.v., but not oral, Bu compared with TBI [18]. A recent prospective cohort analysis in persons with myelodysplastic syndrome, AML, and CML reported better survival after i.v. Bu than with TBI [19].

No prospective or retrospective study has compared Cy in combination with i.v. Bu, oral Bu, or TBI in patients with CML in chronic phase. We used data from CIBMTR to compare outcomes after these regimens.

PATIENTS AND METHODS

Data Sources

The CIBMTR is a working group of more than 500 transplantation centers worldwide that voluntarily contribute data on allogeneic and autologous transplantations. Detailed demographic, disease, and transplantation characteristics and outcome data are collected on a sample of registered patients including all unrelated donor (URD) transplantations facilitated by the National Marrow Donor Program in the United States. Observational studies conducted by the CIBMTR are carried out with a waiver of informed consent and in compliance with Health Insurance Portability and Accountability Act regulations, as determined by the institutional review board and the privacy officer of the Medical College of Wisconsin.

Patients

The study population consisted of all patients ≥18 years of age reported to the CIBMTR who received a first HCT with an HLA-identical sibling or well-matched URD [20] from 2000 through 2006 for CML in first chronic phase after pretransplantation conditioning with Cy/TBI (single dose ≥ 5.5 Gy, fractionated ≥ 9 Gy) or Bu (≥9 mg/kg) combined with Cy and no other anticancer drugs. The data set was derived from CIBMTR comprehensive report forms. Patients with a genetically identical twin or cord blood donor, an ex vivo T cell–depleted graft, a less than well-matched URD, or those receiving Cy after transplantation were excluded. Data regarding Bu pharmacokinetics (PK) were not collected.

Study Endpoints and Definitions

The primary outcome studied was OS. Patients were considered to have an event at the time of death from any cause; survivors were censored at last contact. NRM was defined as death without evidence of leukemia recurrence; relapse, defined by hematologic, cytogenetic, or molecular criteria, was considered a competing event. LFS was defined as time to treatment failure (death or relapse). For relapse, NRM, and LFS, patients alive in continuous complete remission were censored at last follow-up. Times to neutrophil and platelet recovery were calculated as the time from transplantation to achieving the first of 3 consecutive days with neutrophils $>.5 \times 10^9$/L and platelets $>20 \times 10^9$/L, 7 days from the last platelet transfusion. Acute GVHD was graded according to consensus criteria, based on the pattern of severity of abnormalities in skin, gastrointestinal tract, and liver [21]. Chronic GVHD was diagnosed by standard criteria [22]. For hematopoietic recovery and GVHD, death without the event was considered a competing event.

Statistical Methods

In univariate analysis, probabilities of LFS and OS were calculated using the Kaplan-Meier method, with the variance estimated by Greenwood's formula. Hematopoietic recovery, GVHD, NRM, and relapse were estimated using the cumulative incidence method to account for competing risks.

In multivariate analysis, a forward stepwise selection procedure was performed using the proportional hazards Cox model for OS, LFS, NRM, GVHD, and relapse to adjust for the following variables considered for inclusion in each model: age, gender, and Karnofsky performance score at transplantation for subject-related variables; interval from diagnosis to transplantation and TKI use before HCT for disease-related variables, and donor-recipient gender and cytomegalovirus serological status, donor relation and graft source, year of transplantation, antithymocyte globulin (ATG) or alemtuzumab use, GVHD prophylaxis, and planned use of growth factors after transplantation for transplantation-related variables. A P value $<.05$ was used to select variables to enter and to retain as covariates in the model. The proportional hazards assumption was assessed for each variable